959 Clinical Cardiovascular Pharmacology II

Monday, March 17, 1997, 3:00 p.m.–5:00 p.m.
Anaheim Convention Center, Hall E
Presentation Hour: 3:00 p.m.–4:00 p.m.

959-45 The Vasodilator Effects of Cyclic GMP Do Not Explain the Venoselectivity of Nitric Oxide Donors in Humans

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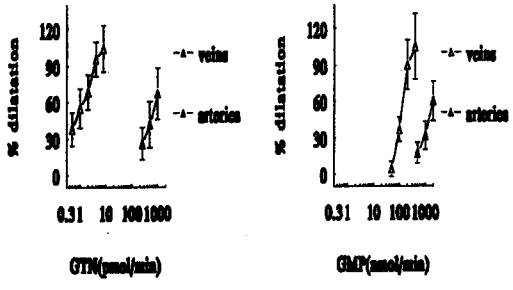
A reduction of the arterial effects of the endogenous dilator, nitric oxide (NO), has been implicated in the development of hypertension and atheroma in humans, and these effects might be reversed by NO-replacement therapy. Currently available NO-donors such as glyceryl trinitrate (GTN) are venoselective, and this limits their usefulness in targeting the arterial circulation. The second messenger for endogenous and exogenous NO is cyclic GMP which is synthesised in the smooth muscle by guanylate cyclase. The aim of this study was to determine whether the venoselectivity of GTN was similar to cyclic GMP. Dose-response curves to GTN or 8-bromocyclic GMP (a stable cyclic GMP analogue) were constructed in preconstricted dorsal hand veins (0.5–8 pmol/min and 50–200 nmol/min, respectively; n = 6) and in the forearm resistance bed (0.25–1 nmol/min and 0.5–2 μmol/min, respectively; n = 6) of healthy volunteers. GTN dilated veins at doses 1000-fold smaller than dilated the forearm vascular bed. In contrast, 8-bromocyclic GMP dilated veins at doses that were 10-fold smaller than those that dilated the forearm resistance bed (Figure).



Arteriovenous profiles of GTN and 8-bromocyclic GMP

Allowing for a 10–20 fold difference between venous and arterial blood flow, these results indicate that cyclic GMP is not venoselective. GTN and other NO donors might be venoselective by stimulating greater cyclic GMP increases in venous than arterial smooth muscle.

959-46 Pharmacodynamics of Basic Fibroblast Growth Factor: Effect of Route of Administration on Regional Distribution

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Our laboratory has shown that basic fibroblast growth factor (bFGF) enhances myocardial collateral development in a canine model of chronic ischemia when delivered via the left atrial (LA) or intracoronary (IC) routes; however, we have found intravenous (IV) bFGF ineffective in the same model. Data on the fate and efficacy of IV bFGF are limited. We hypothesized that first pass lung uptake might limit myocardial bFGF deposition after IV injection, and postulated that delivery of bFGF through the distal port of a wedged Swan Ganz (SG) catheter might circumvent this problem. We therefore evaluated differential regional uptake of I-125 labeled bFGF following bolus IV, SG, LA, IC, and pericardial delivery in fourteen dogs. I-125 activity was assessed 15 and 150 min after injection; percent recovered bFGF was the primary end point. Serum half life of bFGF was comparable after IC, IV and LA delivery (50 min); however, there were significant differences with regard to pharmacodynamics. After IC administration, 3–5% of the total bFGF dose was recovered from the heart, with the peptide immunolocalized to the extracellular matrix and vascular endothelium. In contrast, only 1.3% of the injected bFGF was localized to the heart after LA administration, and 0.5% was recovered after IV or SG delivery. Pericardial administration resulted in the greatest cardiac bFGF delivery; 19% of the injected dose was present at 150 min. These data provide a rationale for the efficacy of IC, LA, and pericardial bFGF for myocardial angiogenesis, and predict a lack of efficacy after bolus IV and SG administration.

959-47 Loop Diuretics Enhanced Secretion of Prostacyclin In Vitro and in Patients with Heart Failure

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Previous studies suggest that the acute hemodynamic effects of loop diuretics are due to a direct dilation on blood vessels, are not related to diuretic properties, but perhaps to prostaglandin secretion. Thus, we firstly investigated whether human endothelial cells responded to torasemide or furosemide with an enhanced secretion of the vasodilator prostaglandin prostacyclin (PGI_2). Moreover, in patients with congestive heart failure (CHF), whose systemic vascular resistance is already high, the venodilator effects of the loop diuretics might be prolonged. Thus, we also investigated whether plasma concentrations of PGI_2 after twenty-five min administration of torasemide or frusemide in twenty-six patients with CHF (NYHA III) were increased. The PGI_2 levels were measured after extraction in ethyl acetate by RIA as levels of 6-Keto-$PGF_{1\alpha}$, a stable metabolite. Data showed that in primary cultured human endothelial cells both frusemide (3×10^{-7} mol/l) and torasemide (10^{-7} mol/l) induced PGI_2 secretion (865 ± 55 and 1250 ± 85* ng/mg of protein, respectively;*$p < 0.05$ vs frusemide) that reached a peak after about five minutes and remained stable for 35 min of continuous exposure of cells to diuretics. In CHF patients, we observed a significant decrease of left ventricular end diastolic pressure in both group of patients after 25 min from the loop diuretic infusion. This effect might be due to a synergism between decrease in plasma volume induced by diuresis and PGI_2 secretion. Basal levels of PGI_2 synthesis were similar between the two groups of CHF patients. However, PGI_2 levels were significantly increased after 25 min of both drug infusion ($p < 0.05$). This increase was significantly higher in patients treated with 10 mg of torasemide than in patients treated with 40 mg of frusemide (155 ± 35* vs 118 ± 29 pg/ml; *$p < 0.05$ vs frusemide).

Thus, our data showed an enhanced secretion of PGI_2 after both torasemide and frusemide administration either *in vitro* or in CHF patients. This phenomenon, which may explain in part the vasodilatory effects of these drugs, was more evident with torasemide and reached at lower concentrations of the drug.

959-48 Monitoring Platelet GPIIb/IIIa-Fibrin Interaction with Tissue Factor-Activated Thromboelastography

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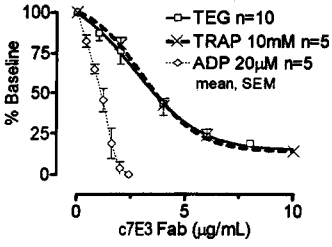
Computerized thromboelastography (TEG) was used to study platelet GPIIb/IIIa function, characterize the consequences of the interaction between polymerizing fibrin and activated platelets, and establish a quantitative assay of platelet function. The ability of platelets to augment the shear elastic modulus of blood clots was measured using TEG under maximal activating conditions during clot formation accelerated by recombinant human tissue factor. Under these conditions, platelets significantly enhance clot strength eight fold. This effect, inhibited by Cytochalasin D and c7E3 Fab, is dependent on the transmission of platelet contractile force to fibrin, via GPIIb/IIIa. The c7E3 Fab dose-response of TF-TEG clot strength is identical to results with platelet aggregation induced by the thrombin receptor agonist peptide ($TRAP_{1-6}$); ADP-induced aggregation is easier to inhibit.



Results obtained with this system are reproducible (CV 4%, r 0.96). As a clinical assay, TEG can be rapidly performed at at the bedside (results in < 30 min), requires only 0.345 ml of unprocessed whole blood, and may offer advantages over conventional measures of platelet function.

MONDAY POSTER